BENZODIAZEPINE HYPNOTICS INCREASE HEART RATE DURING SLEEP

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SUMMARY

Though the cardiovascular action of benzodiazepines, specifically diazepam, has been studied when used as a preoperative sedative, to our knowledge there has been no study that examined the effects of orally administered benzodiazepine hypnotics on cardiovascular activity during sleep. We report the effects of triazolam, 0.5 mg, and flurazepam, 30 mg, on one measure of cardiac activity, heart rate (HR).

Triazolam Study

Twenty EEG-screened male poor sleepers, mean age 21 ± 2.4 years, were studied during 3 placebo, 6 treatment, and 2 withdrawal nights. On treatment nights, 10 subjects received triazolam and 10 placebo. These nights were double-blind and HR analysis was also blind. HR was analyzed for placebo baseline night 1, treatment nights 1 and 3, and the 2 withdrawal nights. Subjects were continuously recorded in bed from 2200 to 0530. Heart beats were counted visually for 30-second samples every 3 minutes on each night.

Analysis: Average HR was calculated for total night and for each hour of the night independent of sleep stage. In a second step, the average HR was calculated for each REM period and for the 30-minute NREM period that immediately preceded each REM. Between- and within-group comparisons were made for change in HR during treatment compared to placebo baseline and withdrawal.

Results: There was no significant difference between groups for HR on placebo baselines. In the drug group, average HR increased on drug nights with the maximum increase occurring during the first half of the night. Between- and within-group t-tests showed the increase in all-night HR was significant for drug night 1 but not for night 3. During the first 4 hours of sleep, the average HR increase on drug night 1 was 4.5 bpm, and on night 3 it was 3.0 bpm.

REM/NREM: In the drug group, there was an increase of the average HR in both REM and NREM during the 2 drug nights, but the average increase was significantly larger during NREM, 4.7 vs. 2.9 bpm.

Flurazepam Study

The HR for 6 Dalmane subjects from a previous study was obtained on the 6th placebo baseline night and 5th drug night. Heart beats, recorded on FM tape, were analyzed by computer. HR during the drug night was significantly higher, average increase 5.4 bpm, during the first 4.5 hours of sleep when compared to placebo baseline.

The average 4.5—5.4 bpm increase is consistent with the 4—6 bpm changes within 20 to 30 minutes after intravenous injection of diazepam. Finding the diazepam-related HR increase in patients after sympathetic blocking suggests that HR elevation is the result of peripheral vasodilation.

INTRODUCTION

Though the cardiovascular action of benzodiazepines, when used as preoperative sedatives, has been studied, to our knowledge there has been no study that examined the effects of orally administered benzodiazepine hypnotics on cardiovascular activity during sleep. We report the effects of triazolam (0.5 mg) and flurazepam (30 mg) on one measure of cardiac activity, heart rate (HR), during sleep. Our findings demonstrate that oral administration significantly increases HR when compared to placebo-baseline levels and to subjects receiving placebo.

Sedative doses of benzodiazepines, such as diazepam and lorazepam, produce a moderate decrease in left ventricular stroke work, stroke volume, and cardiac output. As a consequence of these changes, there is a decrease in systolic blood pressure and reflexivity, and an increase in systemic peripheral resistance and HR.[1,2] The increase in HR is usually reported as mild, 4 to 10 bpm, but statistically significant, and the increase persists 20 to 25 minutes after intravenous administration.[3-5] Though other significant cardiovascular changes are reported, the HR increase has not always reached statistically significant levels.[6-8]

The hypnotic effects of the benzodiazepines are attributed to the actions of these drugs on the central nervous system (CNS). The sedative-hypnotic effects are reflected in decreased sleep latency and increased total sleep time. There is also a significant increase in arousal threshold.[9-11] The CNS effects are also seen in the significant changes in electroencephalographic (EEG) activity, a decrease in delta activity and an increase in sleep spindles.[12-14] Thus, the general view has been that the effects of benzodiazepines, when taken orally in hypnotic-dose levels, result from actions on the CNS. Because of the pronounced CNS effects, the effects of benzodiazepines on peripheral tissue, such as vasodilation seen in intravenous administration, usually are not marked and have not been examined in the sleeping subject. An oral hypnotic dose of triazolam produced no cardiovascular changes in a study of hemodynamic effects in awake subjects.[15] However, in a study of the effects of triazolam on vascular smooth muscles and its reflex control in awake subjects, Elliott *et al.*[7] reported drug effects were most apparent in HR measurements. At doses of 0.5 mg or more, the average HR increase was 7 and 24 beats after 0.75 to 1 hour and 3 to 4 hours, respectively. Perhaps because there is a decrease in HR with sleep onset, it was not expected that the HR of the more deeply sleeping benzodiazepine subjects would be higher than those of the unmedicated sleepers.

Data were obtained from two studies: one using 0.5 mg of triazolam (Halcion) and the other, 30 mg of flurazepam (Dalmane).

Triazolam Study

Subjects were 20 male poor sleepers (mean age 21 years) with EEG-measured sleep latencies longer than 30 minutes. All subjects were given a placebo for 3 consecutive nights (single-blind). Then 10 continued to receive placebo while 10 were given 0.5 mg triazolam for 6 consecutive treatment nights (double-blind). Finally, all 20 subjects received placebo on 2 withdrawal nights (single-blind). Sleep stage scoring was according to the Rechtschaffen and Kales manual.[16]

Nights 2, 5, 7, 11, and 12 were chosen for the HR analysis in the two groups, as the subjects' sleep was uninterrupted by other procedures on these nights. Subjects were continuously recorded from 2200 to 0530. Thirty artifact-free seconds of heart beats were counted visually on

the records during every 3 minutes for the baseline (N2), the treatment (N5 and N7), and the withdrawal (N11 and N12) nights, for all 20 subjects. These 30-second samples were averaged for each hour. In a first step, an average HR was calculated for each hour of the night without regard to sleep stages. In a second step, an average HR was calculated for each rapid eye movement (REM) phase longer than 8 minutes, and for the 30-minute nonREM (NREM) period which immediately preceded that REM phase. REM phases were of variable durations, but, on the average, they were close to 30 minutes. Therefore, we chose a fixed NREM period with a 30-minute duration. The NREM period and the subsequent REM period constituted a REM-NREM epoch. Dependent and independent Student's t-tests were used, and $P < .05$, two-tailed, was accepted as significant.

In Fig. 1 are the average HR values for the triazolam and placebo groups for the entire night and for the first 4 hours and the final 3.5 hours of sleep for the 5 study nights. Though there was no significant difference in mean HR between the two groups on the baseline night, difference score values (treatment minus baseline) were used for between-groups comparison to control for baseline differences that were present.
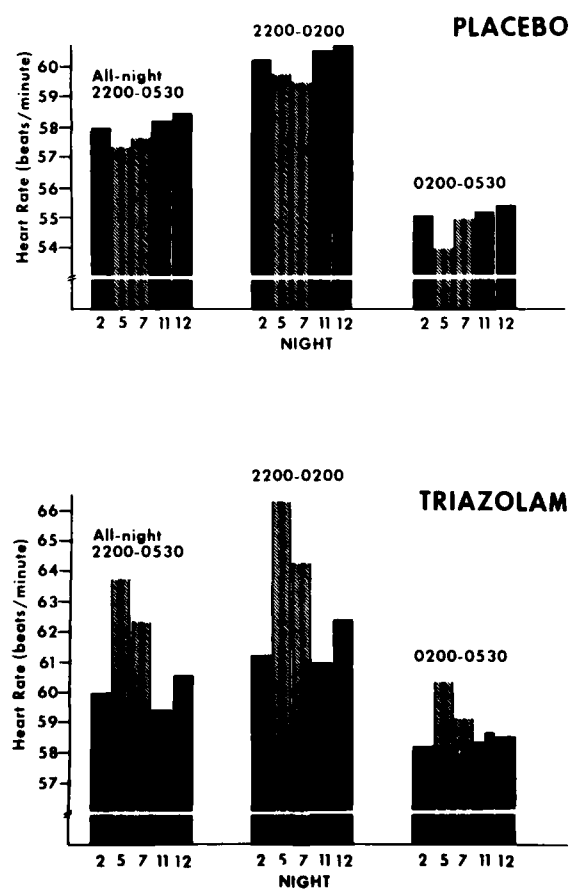

Fig. 1.   Mean HR (bpm) for the entire night (all night), and for first half (2200-0200) and last half (0200-0530) of sleep for placebo and triazolam subjects on night 2 (placebo-baseline), nights 5 and 7 (treatment), and nights 11 and 12 (placebo-withdrawal).

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In the triazolam group, when compared to baseline, HR increased on treatment nights, with the maximum increase occurring during the first half of the night. Between- and within-group t-tests showed that the increase in all-night HR was significant for the first night of drug administration (night 5), but not for the third drug night (night 7): between-groups t_{18} = 2.27, $P < .05$, within (drug group) t_9 = 2.67, $P < .05$ for night 5. For night 7, the respective t values were 1.10 and 1.79.

When the 2200 to 0200 hours and 0200 to 0530 hours time periods were compared to the same baseline times, there was no significant change in HR during the 0200 to 0530 time period. For the first 4 hours, both between- and within-group comparisons showed a significant HR increase on night 5 (between-groups t_{18} = 2.40, within (drug group) t_9 = 1.99), but the increased failed to reach the .05 two-tail probability level on night 7. During the first 4 hours of sleep on night 5, the average HR increase over baseline was 4.86 ± 5.18 and on night 7 it was 2.98 ± 1.94.

Analysis of the HR during REM, and for the 30 minutes of NREM before each REM period, indicated that the average increase in HR was significantly larger during NREM in the triazolam subjects. This increase erased the usually higher HR during REM sleep during treatment nights for the subjects receiving triazolam. These results are illustrated in Fig. 2. Note that in the drug group during the third REM cycle, the expected higher REM HR is present, especially on night 7. For the first REM cycle on night 5, the average increase in HR was 4.7 bpm for NREM and 2.9 bpm for REM, and 4.6 bpm NREM and 2.7 bpm REM for the night 7 first REM-NREM epoch. The HR during withdrawal was similar to that on baseline.

Flurazepam Study

To see if the HR increase found was also present in our earlier study on 30 mg flurazepam, we analyzed our HR data for the 6 subjects who received flurazepam. These subjects were comparable to those in the triazolam study. The study was also a 3-phase design; 7 placebo-baseline, 10 treatment nights, and 3 placebo-withdrawal nights 2 weeks after the last treatment night. Six subjects received placebo capsules during the entire study, while the 6 subjects, whose HR data are reported here, received flurazepam during the treatment period.

For this study, the heart beats were recorded on FM tape, and the beat-by-beat analysis for placebo-baseline night 6 and the fifth drug night was done off-line by computer. The sleep on these nights was uninterrupted by other study procedures. The beat-by-beat analysis was done for the first 4.5 hours of sleep, as complete data were not available on all 6 subjects for the last 3 hours of sleep due to problems in changing to a second tape reel. Inspection of the bpm printout in the subjects with data for the total night indicated no difference between placebo-baseline and treatment nights for the last 3.5 hours of sleep.

Student's t-tests for correlated means indicated that HR was significantly higher during the drug night when compared to placebo-baseline, t_5 = 5.12, $P < .01$. HR increase was also significant, t_5 = 5.58, $P < .01$, when the drug night was compared with the HR during the first placebo-withdrawal night. The mean HR increase over placebo-baseline during the first 4.5 hours of sleep on the drug night was 5.4 ± 5.12 bpm.

Oral administration of hypnotic dose levels of two benzodiazepines produces a similar magnitude of HR increase as seen in sedative dose levels given intravenously. While the magnitude
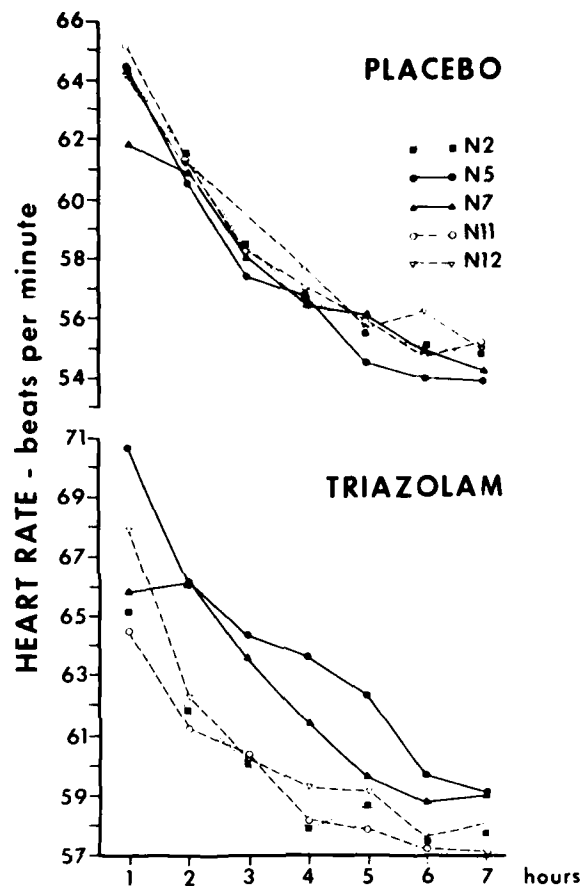
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Fig. 2. Comparison of REM-NREM epochs HR (bpm) for placebo and tria-
zolam subjects on night 2 (placebo-baseline), nights 5 and 7
(treatment), and nights 11 and 12 (placebo-withdrawal).

of the change is similar, the duration of the change is longer during sleep, lasting 3 to 4 hours,
in contrast to less than 1 hour when given as a sedative.

The HR change is almost identical for the two benzodiazepines, with the exception being the
number of nights over which the elevation in HR remains statistically significant. By the third
night of drug administration, the triazolam subjects were developing a tolerance and the HR
increase, though still present, was not significantly different from baseline. In contrast, for
subjects taking flurazepam the HR increase was significantly elevated over baseline on the fifth
drug night. Similar differences between the two drugs have been found for EEG changes. By the
third drug night, the increase in sleep spindles and decrease in delta were beginning to plateau
in the 0.5 mg triazolam subjects, but, for subjects taking 30 mg flurazepam, spindle count was
still increasing and delta count was continuing to decrease after 9 nights of flurazepam use.[12]
The indication of tolerance development with triazolam and, contrastingly, the evidence of cumula-
tive effects with flurazepam, may be explained by different pharmacokinetic properties of the two

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drugs. Since triazolam is short-acting, having a half-life as short as 5 hours, and flurazepam has an active metabolite with a half-life of over 24 hours,[17] the effects of consecutive nights of administration should differ for the two drugs.

The mechanism for the cardiovascular changes produced by the benzodiazepines is not completely known. Changes in baroreceptor sensitivity were not indicated in a study by Markiewicz *et al.*[4] Whether the effect of the benzodiazepines on cardiac function is extended directly on the heart and peripheral vessels, or whether it is mediated through the autonomic system, was investigated by Côté *et al.*[3] Partial autonomic blockage was induced in 10 patients by the intravenous administration of 5 mg propanolol and 0.8 mg atropine. Five minutes later, diazepam (0.1 mg/kg of body weight) was administered intravenously over a 1-minute period. The authors report that the primary systemic hemodynamic effects of diazepam still occurred in the presence of autonomic nervous blockage. Côté *et al.* thus concluded that their results demonstrate that diazepam produces peripheral vascular smooth muscle dilation in spite of partial sympathetic or parasympathetic blockage.

Though the increase in HR during sleep when a benzodiazepine is taken is statistically significantly higher than on nondrug nights, the magnitude of the increase does not appear to be clinically significant for most patients. However, this HR finding, along with the reports of anterograde amnesia following oral administration at bedtime,[11,18-20] indicates that these benzodiazepine effects, once thought to be short-lived and specific to intravenous administration in sedative-dose levels, can occur with oral administration and the effects can persist for hours. Accepting the findings by Côté *et al.*, these results suggest that the benzodiazepines, when used in hypnotic-dose levels, not only act directly on the CNS, but also act directly on smooth muscles causing vasodilation. This peripheral effect is more pronounced during NREM sleep.

REFERENCES

1. Elliott, H.W., N. Nomof, G. Navarro, H.W. Ruelius, J.A. Knowles, & W.H. Comer. Central nervous system and cardiovascular effects of lorazepam in man. *Clinical Pharmacology & Therapeutics,* 1971, 12: 468-481.

2. Rao, S., R.W. Sherbaniuk, K. Prasad, S.J.K. Lee, & B.J. Sproule. Cardiopulmonary effects of diazepam. *Clinical Pharmacology & Therapeutics,* 1973, 14: 182-189.

3. Côté, P., J. Noble, & M.G. Bourassa. Systemic vasodilatation following diazepam after combined sympathetic and parasympathetic blockade in patients with coronary heart disease. *Catheterization & Cardiovascular Diagnosis,* 1976, 2: 369-380.

4. Markiewicz, W., S. Hunt, D.C. Harrison, & E.L. Alderman. Circulatory effects of diazepam in heart disease. *Journal of Clinical Pharmacology,* 1976, 16: 637-644.

5. Allen, G.D., G.B. Everett, & L.A. Butler. Human cardiorespiratory and analgesic effects of intravenous diazepam and local anesthesia. *Journal of the American Dental Association,* 1976, 92: 744-747.

6. Côté, P., P. Guéret, & M.G. Bourassa. Systemic and coronary hemodynamic effects of diazepam in patients with normal and diseased coronary arteries. *Circulation*, 1974, 50: 1210-1216.

7. Elliott, H.W., G. Navarro, N. Kokka, & N. Nomof. Early Phase I evaluation of sedatives, hypnotics or minor tranquilizers. In F. Kagan, T. Harwood, K. Rickels, A.D. Rudzik, & H. Sorer (Eds.), *Hypnotics. Methods of Development and Evaluation*. New York: Spectrum, 1975. Pp. 87-105.

8. Pozenel, H., A. Bückert, & R. Amrein. The antihypertensive effect of LEXOTAN (bromazepine)-- a new benzodiazepine derivative. *International Journal of Clinical Pharmacology & Biopharmacology*, 1977, 15: 31-39.

9. Church, M.W. & L.C. Johnson. Mood and performance of poor sleepers during repeated use of flurazepam. *Psychopharmacology*, 1979, 61: 309-316.

10. Bonnet, M.H., L.C. Johnson, & W.B. Webb. The reliability of arousal threshold during sleep. *Psychophysiology*, 1978, 15: 412-416.

11. Spinweber, C.L. & L.C. Johnson. Effects of triazolam (0.5 mg) on sleep, performance, memory, and arousal threshold. *Psychopharmacology*, in review.

12. Johnson, L.C., D.M. Seales, P. Naitoh, M.W. Church, & M. Sinclair. The effects of flurazepam hydrochloride on brain electrical activity during sleep. *Electroencephalography & Clinical Neurophysiology*, 1979, 47: 309-321.

13. Johnson, L.C. & C.L. Spinweber. Effects of a short-acting benzodiazepine on brain electrical activity during sleep. *Electroencephalography & Clinical Neurophysiology*, in press.

14. Feinberg, I., G. Fein, J.M. Walker, L.J. Price, T.C. Floyd, & J.D. March. Flurazepam effects on slow-wave sleep: Stage 4 suppressed but number of delta waves constant. *Science*, 1977, 198: 847-848.

15. Knapp, R., D. Remen, G. Linsenmeyer, & E. Boyd. An evaluation of the cardiopulmonary safety and efficacy of triazolam, flurazepam, and placebo as oral hypnotic agents. *Clinical Pharmacology & Therapeutics*, 1977, 21: 107-108. (Abstract)

16. Rechtschaffen, A. & A. Kales (Eds.). *A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects*. Washington, D.C.: Government Printing Office, 1968.

17. Goodman, A.G., L.S. Goodman, & A. Gilman (Eds.). *The Pharmacological Basis of Therapeutics*. New York: Macmillan, 6th Ed., 1980.

18. Bixler, E.O., M.B. Scharf, C.R. Soldatos, D.J. Mitsky, & A. Kales. Effects of hypnotic drugs on memory. *Life Sciences*, 1979, 25: 1379-1388.

19. Veldkamp, W., R.N. Straw, C.M. Metzler, & H.V. Demissianos. Efficacy and residual effect evaluation of a new hypnotic, triazolam. *Journal of Clinical Pharmacology*, 1974, 14: 102-111.

20. Roth, T., K.M. Hartse, P.G. Saab, P.M. Piccione, & M. Kramer. The effects of flurazepam, lorazepam, and triazolam on sleep and memory. *Psychopharmacology*, 1980, 70: 231-237.

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(U) Intravenous administration of benzodiazepines as preoperative sedatives produces cardiovascular changes including a short-lived elevation in heart rate (HR). Bedtime oral administration of triazolam (0.5 mg) and flurazepam (30 mg) was found to cause a HR increase of similar magnitude which was present during the first 4 hours of sleep. This peripheral effect was unexpected in view of the CNS sleep-promoting properties of benzodiazepine hypnotics.
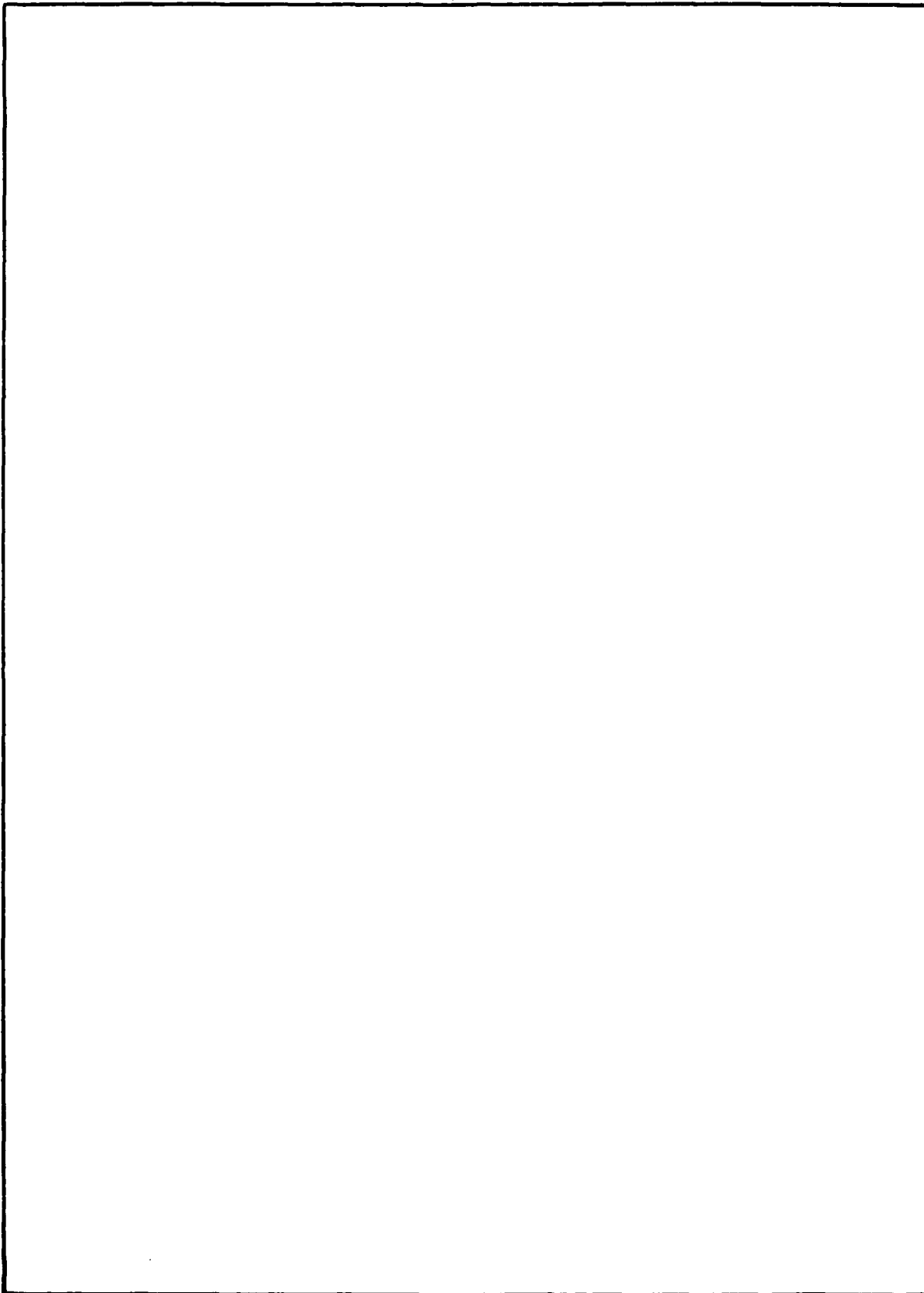
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